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EXAMINER	
BRUSCA, JOHN S	

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1631	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	08/808,827	GUNZBURG ET AL.	
	Examiner	Art Unit	
	John S. Brusca	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,7,10-17,19-26,28,29,31-35,37-43,45-58,60-66 and 68-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5, 7, 10-17, 19-26, 28, 29, 31-35, 37-43, 45-58, 60-66, and 68-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1, 5, 7, 10-17, 19-26, 28, 29, 31-35, 37-43, 45-58, 60-66, and 68-78 are pending. Claims 1, 5, 7, 10-17, 19-26, 28, 29, 31-35, 37-43, 45-58, 60-66, and 68-78 are rejected.

Claim Objections

2. Claims 20 and 21 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claims depend from a subsequent claim. The claim set should be amended so that the subject matter of claims 20 and 21 are not in a dependent claim that depends from a subsequent claim.

3. Claim 24 is objected to because of the following informalities: The claim recites the term "encoding" and should be amended to recite "encoded.". Appropriate correction is required.

Double Patenting

4. The rejection of claims 1, 5, 16, 17, 22, 28, 29, 31, and 32 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 8 of U.S. Patent No. 6,177,681 in the Office action mailed 26 September 2007 is withdrawn in view of the amendment filed 10 December 2007.

5. The rejection of claims 1, 5, 11, 12, and 22 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 20 of U.S. Patent No. 6,730,511 in the Office action mailed 26 September 2007 is withdrawn in view of the amendment filed 10

December 2007 and the limitation of placement of the naf open reading frame downstream of the 5' LTR in the vector of U.S. Patent No. 6,730,511, which is not obvious from the instant claimed invention.

6. The rejection of claims 1, 5, 11, 17, 20-25, 28, and 29 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 7,022,319 in the Office action mailed 26 September 2007 is withdrawn in view of the amendment filed 10 December 2007.

7. The rejection of claims 1, 5, 7, 20-22, 26, 28, 29, 31-35, 38, 42, 43, 46, 50, 51, 54-58, 61, 65, 66, 69, 73, 74, 77, and 78 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 8-13, 16-18, 20, 21, and 24-28 of U.S. Patent No. 7,074, 398 in the Office action mailed 26 September 2007 is withdrawn in view of the amendment filed 10 December 2007.

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225

USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 1, 5, 11, 15, 16, 17, 22, 28, 29, 31, and 32 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8 and 10 of U.S. Patent No. 6,177,681.

The claims are drawn to a murine leukemia virus vector with a partially deleted U3 region in which is inserted a polylinker comprising a heterologous promoter. In some embodiments the vector comprises a regulatory element regulatable by transacting molecules, a marker gene, a cellular sequence, and a target cell specific promoter. In some embodiments the vector is in a kit further comprising a packaging cell. Some embodiments are drawn to retroviral particles produced by packaging cells infected with the vector or a packaging cell infected with the vector.

Claims 8 and 10 of U.S. Patent No. 6,177,681 show a packaging cell line infected with a murine leukemia virus vector with a partially deleted U3 region in which is inserted a polylinker comprising a heterologous promoter or regulatory element that is target cell specific or regulatable by transacting molecules. In some embodiments the vector comprises a marker gene or coding sequences that are from cellular genes.

Claims 8 and 10 of U.S. Patent No. 6,177,681 do not show a kit comprising a packaging cell and a vector as claimed in instant claim 17, or retroviral particles as claimed in instant claims 22 and 29.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a kit of the packaging cell and vector because such a kit would allow for convenience in infecting the packaging cell with the vector. It would have been further obvious to collect retroviral particles produced by the infected packaging cell for the purpose of subsequently infection of host cells.

10. Claim 7 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 8 of U.S. Patent No. 6,177,681 in view of Mee et al.

The claim is drawn to a murine leukemia virus vector with a partially deleted U3 region in which is inserted a polylinker comprising a mouse mammary tumor virus promoter (MMTV) promoter.

Claim 8 of U.S. Patent No. 6,177,681 show a packaging cell line infected with a murine leukemia virus vector with a partially deleted U3 region in which is inserted a polylinker comprising a heterologous promoter.

Claim 8 of U.S. Patent No. 6,177,681 does not show a vector comprising an MMTV promoter.

Mee et al. shows a retroviral vector comprising a mouse mammary tumor virus LTR, and that the LTR expressed a gene after induction with dexamethasone. Mee et al. state on page 292 that their vector is a potentially powerful tool for the manipulation of gene expression in a variety of cell types.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of claim 8 of U.S. Patent No. 6,177,681 by insertion of an MMTV promoter region in a deleted 3' U3 region of a retroviral vector because Mee et al. show that their LTR promoter may be used to manipulate gene expression in a variety of cell types.

11. Claims 10 and 12 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8 and 10 of U.S. Patent No. 6,177,681 in view of Price et al.

The claim is drawn to a murine leukemia virus vector with a partially deleted U3 region in which is inserted a polylinker comprising a heterologous promoter, and further comprising a beta galactosidase reporter gene or in which the vector is derived from a BAG vector.

Claims 8 and 10 of U.S. Patent No. 6,177,681 show a packaging cell line infected with a murine leukemia virus vector with a partially deleted U3 region in which is inserted a polylinker comprising a heterologous promoter. In some embodiments the vector comprises a marker gene.

Claims 8 and 10 of U.S. Patent No. 6,177,681 do not show a vector that is a BAG vector or a vector that comprises a beta galactosidase reporter gene.

Price et al. shows a BAG retroviral vector comprising a beta galactosidase reporter gene, and that the vector can be used to identify cells and progeny of cells infected with the vector.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of claims 8 and 10 of U.S. Patent No. 6,177,681 by basing the construction on a BAG vector of Price et al. because Price et al shows that a vector with a beta-galactosidase reporter gene may be used to identify cells and progeny of cells infected with the vector.

12. Claims 13 and 14 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 8 of U.S. Patent No. 6,177,681 in view of Miller et al. in view of Panganiban '84.

The claims are drawn to a retroviral vector comprising an altered retroviral gene or a partially deleted sequence involved in integration of retroviruses.

Claim 8 of U.S. Patent No. 6,177,681 show a packaging cell line infected with a murine leukemia virus vector with a partially deleted U3 region in which is inserted a polylinker comprising a heterologous promoter.

Claim 8 of U.S. Patent No. 6,177,681 does not show an altered retroviral gene or a partially deleted sequence involved in integration of retroviruses.

Miller et al. shows in the introduction on page 980 that it is desirable to have retroviral vectors that cannot recombine with retroviral sequences in packaging cell lines to yield

contaminating helper virus. In figure 2 Miller et al. shows that extensive deletions in their retroviral vectors to block recombination with packaging cell line retroviral sequences, including deletion of the pol gene, but that their vectors retain the phi+ packaging sequence.

Panganiban '84 shows that the 3' end of the pol gene encodes the int locus that is required for integration of the reverse transcribed retroviral genome to form a provirus.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to include a deletion of at least the pol gene in the retroviral vector of claim 8 of U.S. Patent No. 6,177,681 because Miller et al. shows that prevention of recombination with packaging cell retroviral sequences is desirable and may be achieved by deletion of viral genes, including the pol gene. Panganiban '84 shows that deletion of the pol gene also deletes the integration site, as claimed in instant claim 14.

13. Claims 33-35, 38, 42, 43, 46-49, and 51-55 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8 and 10 of U.S. Patent No. 6,177,681 in view of Mehigh et al.

The claims are drawn to a murine leukemia virus vector with a partially deleted U3 region in which is inserted a polylinker comprising a cellular promoter. In some embodiments the vector comprises a regulatory element regulatable by transacting molecules, a marker gene, a cellular sequence, a target cell specific promoter, or a whey acidic protein promoter. In some embodiments the vector is in a kit further comprising a packaging cell. Some embodiments are drawn to retroviral particles produced by packaging cells infected with the vector or a packaging cell infected with the vector.

Claims 8 and 10 of U.S. Patent No. 6,177,681 show a packaging cell line infected with a murine leukemia virus vector with a partially deleted U3 region in which is inserted a polylinker comprising a heterologous promoter or regulatory element that is target cell specific or regulatable by transacting molecules. In some embodiments the vector comprises a marker gene or coding sequences that are from cellular genes.

Claims 8 and 10 of U.S. Patent No. 6,177,681 do not show a kit comprising a packaging cell and a vector, or retroviral particles as claimed in instant claims 22 and 29, or retroviral vectors comprising a cellular whey acidic protein promoter.

Mehigh et al. shows a retroviral vector comprising a whey acidic acid protein (WAP) promoter. Mehigh et al. states in the abstract that their vector allows for inducible expression from the WAP promoter of an operably linked gene in MBDK cells and may prove useful as a delivery system for peptides in cattle to increase milk production.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of claims 8 and 10 of U.S. Patent No. 6,177,681 by insertion of a WAP promoter region in a deleted 3' U3 region of a retroviral vector because Mehigh et al. shows that such vectors are inducibly expressed and may allow for increased milk production in cattle.

14. Claims 19, 20, 21, 23-25, 56, 57, 61, 65, 66, 68-72, and 74-78 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8 and 10 of U.S. Patent No. 6,177,681 in view of Couture et al.

The claims are drawn to a murine leukemia virus vector with a partially deleted U3 region in which is inserted a polylinker comprising a heterologous promoter. In some embodiments the vector comprises a regulatory element regulatable by transacting molecules, a marker gene, a cellular sequence, or a heterologous retroviral promoter. In some embodiments the vector is in a kit further comprising a packaging cell. Some embodiments are drawn to retroviral particles produced by packaging cells infected with the vector or a packaging cell infected with the vector, or a provirus produced by the vector after infection. In some embodiments the packaging cell lines are PA317 or GP&E86.

Claims 8 and 10 of U.S. Patent No. 6,177,681 show a packaging cell line infected with a murine leukemia virus vector with a partially deleted U3 region in which is inserted a polylinker comprising a heterologous promoter or regulatory element that is target cell specific or regulatable by transacting molecules. In some embodiments the vector comprises a marker gene or coding sequences that are from cellular genes.

Claims 8 and 10 of U.S. Patent No. 6,177,681 do not show a kit comprising a packaging cell and a vector, or retroviral particles, or packaging cell lines PA317 or GP&E86, or explicitly a provirus in an infected cell, or a vector comprising a heterologous retroviral promoter.

Couture et al. (Reference AS in the Form PTO-1449 filed 9/23/97) shows retroviral vectors comprising a substitution of a portion of the 3' U3 region with the corresponding region of 5 different murine retroviruses, including leukemia and sarcoma retroviruses. Couture et al. shows in the abstract that the inserted region comprises an enhancer regulatory element and a promoter. Couture et al. shows on page 669 column 2 that the first 40 nucleotides of the original

vector are retained in the substitution of the U3 region. The vector of Couture comprises a chloramphenicol acetyl transferase marker gene operably linked to the recombinant reporter and a neomycin resistance gene. Couture et al. shows in the abstract that after packaging, the substituted U3 region appears at the 5' LTR and serves as a promoter for all genes in the body of the vector, and that different LTR constructs were preferentially expressed in specific cell types. Couture et al. states in the second paragraph of the Results section on page 669 that U3 regions are bound by cellular factors. Couture et al. shows in Table 3 that their chimeric LTR promoters are active in a cell type specific manner. Couture et al. state on page 670 that promoter suppression or interference may occur within retroviral vectors containing internal promoter elements. Couture et al. states on page 667 that retroviral vectors with target cell specificity have utility in gene therapy protocols. Couture et al. shows the use of packaging cell lines PA317 and GP&E86 on page 669 to package their retroviral vectors into retroviral particles. Couture et al. show on page 668, at the top of the first column that retroviral expression controlled by the LTR occurs after integration of a provirus in infected cells.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vectors of claims 8 and 10 of U.S. Patent No. 6,177,681 by addition of a heterologous retroviral promoter because Couture et al. shows that such retroviral vectors allow for control of the cell type in which the vector genes are expressed. It would have been further obvious to make a kit of the packaging cell and vector because such a kit would allow for convenience in infecting the packaging cell with the vector. It would have been further obvious to collect retroviral particles produced by the infected packaging cell for the purpose of

subsequently infection of host cells. It would have been further obvious to use the packaging cell lines PA317 and GP&E86 on page 669 to package their retroviral vectors into retroviral particles because Couture et al. show that those packaging cell lines are useful to package retroviral vectors.

15. Claim 26 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8 and 10 of U.S. Patent No. 6,177,681 in view of Longmore et al. and Kay et al.

The claims are drawn to a murine leukemia virus vector particle with a partially deleted U3 region in which is inserted a polylinker comprising a heterologous promoter. The vector can be used as a therapeutic composition.

Claims 8 and 10 of U.S. Patent No. 6,177,681 show a packaging cell line infected with a murine leukemia virus vector with a partially deleted U3 region in which is inserted a polylinker comprising a heterologous promoter or regulatory element that is target cell specific or regulatable by transacting molecules.

Claims 8 and 10 of U.S. Patent No. 6,177,681 do not show a vector that can be used as a therapeutic composition.

Longmore et al show in the abstract that mice infected with a retroviral vector expressing the erythropoietin receptor had increased platelet counts and splenic megakaryocytes.

Kay et al. shows in the abstract and throughout that hemophiliac dogs infected with a retroviral vector expressing factor IX shows improved levels of clotting and thromboplastin times for greater than 5 months after treatment.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of claims 8 and 10 of U.S. Patent No. 6,177,681 to express a therapeutic protein because both Kay et al. and Longmore et al. show that retroviral vectors may be used to express therapeutically effective levels of a recombinant protein in an animal.

16. Claims 37 and 39 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8 and 10 of U.S. Patent No. 6,177,681 in view of Mehigh et al. as applied to claims 33-35, 38, 42, 43, 46-49, and 51-55 above and further in view of Price et al.

The claims are drawn to retroviral vectors that are derived from a BAG vector or comprise a beta-galactosidase gene.

Claims 8 and 10 of U.S. Patent No. 6,177,681 in view of Mehigh et al. as applied to claims 33-35, 38, 42, 43, 46-49, and 51-55 above do not show a retroviral vector derived from a BAG vector or comprising a beta-galactosidase gene.

Price et al. shows a BAG retroviral vector comprising a beta galactosidase reporter gene, and that the vector can be used to identify cells and progeny of cells infected with the vector.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of claims 8 and 10 of U.S. Patent No. 6,177,681 in view of Mehigh et al. as applied to claims 33-35, 38, 42, 43, 46-49, and 51-55 above by basing the construction on a BAG vector of Price et al. because Price et al shows that a vector with a

beta-galactosidase reporter gene may be used to identify cells and progeny of cells infected with the vector.

17. Claims 40 and 41 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8 and 10 of U.S. Patent No. 6,177,681 in view of Mehigh et al. as applied to claims 33-35, 38, 42, 43, 46-49, and 51-55 above and further in view of Miller et al and Panganiban et al.

The claims are drawn to retroviral vectors that comprise an altered retroviral gene or a partially deleted sequence involved in integration of retroviruses.

Claims 8 and 10 of U.S. Patent No. 6,177,681 in view of Mehigh et al. as applied to claims 33-35, 38, 42, 43, 46-49, and 51-55 above do not show retroviral vectors that comprise an altered retroviral gene or a partially deleted sequence involved in integration of retroviruses.

Miller et al. shows in the introduction on page 980 that it is desirable to have retroviral vectors that cannot recombine with retroviral sequences in packaging cell lines to yield contaminating helper virus. In figure 2 Miller et al. shows that extensive deletions in their retroviral vectors to block recombination with packaging cell line retroviral sequences, including deletion of the pol gene, but that their vectors retain the phi+ packaging sequence.

Panganiban '84 shows that the 3' end of the pol gene encodes the int locus that is required for integration of the reverse transcribed retroviral genome to form a provirus.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to include a deletion of at least the pol gene in the retroviral vector of claims 8 and 10 of U.S. Patent No. 6,177,681 in view of Mehigh et al. as applied to claims 33-35, 38,

42, 43, 46-49, and 51-55 above because Miller et al. shows that prevention of recombination with packaging cell retroviral sequences is desirable and may be achieved by deletion of viral genes, including the pol gene. Panganiban '84 shows that deletion of the pol gene also deletes the integration site.

18. Claim 45 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8 and 10 of U.S. Patent No. 6,177,681 in view of Mehigh et al. as applied to claims 33-35, 38, 42, 43, 46-49, and 51-55 above and further in view of Couture et al.

Claims 8 and 10 of U.S. Patent No. 6,177,681 in view of Mehigh et al. as applied to claims 33-35, 38, 42, 43, 46-49, and 51-55 above do not show a kit comprising packaging cell lines PA317 or GP&E86.

Couture et al. (Reference AS in the Form PTO-1449 filed 9/23/97) shows retroviral vectors comprising a substitution of a portion of the 3' U3 region with the corresponding region of 5 different murine retroviruses, including leukemia and sarcoma retroviruses. Couture et al. shows in the abstract that the inserted region comprises an enhancer regulatory element and a promoter. Couture et al. shows on page 669 column 2 that the first 40 nucleotides of the original vector are retained in the substitution of the U3 region. The vector of Couture comprises a chloramphenicol acetyl transferase marker gene operably linked to the recombinant reporter and a neomycin resistance gene. Couture et al. shows in the abstract that after packaging, the substituted U3 region appears at the 5' LTR and serves as a promoter for all genes in the body of the vector, and that different LTR constructs were preferentially expressed in specific cell types. Couture et al. states in the second paragraph of the Results section on page 669 that U3 regions

are bound by cellular factors. Couture et al. shows in Table 3 that their chimeric LTR promoters are active in a cell type specific manner. Couture et al. state on page 670 that promoter suppression or interference may occur within retroviral vectors containing internal promoter elements. Couture et al. states on page 667 that retroviral vectors with target cell specificity have utility in gene therapy protocols. Couture et al. shows the use of packaging cell lines PA317 and GP&E86 on page 669 to package their retroviral vectors into retroviral particles. Couture et al. show on page 668, at the top of the first column that retroviral expression controlled by the LTR occurs after integration of a provirus in infected cells.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vectors of claims 8 and 10 of U.S. Patent No. 6,177,681 in view of Mehigh et al. as applied to claims 33-35, 38, 42, 43, 46-49, and 51-55 above by use of the packaging cell lines PA317 and GP&E86 on page 669 to package their retroviral vectors into retroviral particles because Couture et al. show that those packaging cell lines are useful to package retroviral vectors.

19. Claim 50 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8 and 10 of U.S. Patent No. 6,177,681 in view of Mehigh et al. as applied to claims 33-35, 38, 42, 43, 46-49, and 51-55 above and further in view of Longmore et al. and Kay et al.

Claims 8 and 10 of U.S. Patent No. 6,177,681 in view of Mehigh et al. as applied to claims 33-35, 38, 42, 43, 46-49, and 51-55 above do not show a vector that can be used as a therapeutic composition.

Longmore et al show in the abstract that mice infected with a retroviral vector expressing the erythropoietin receptor had increased platelet counts and splenic megakaryocytes.

Kay et al. shows in the abstract and throughout that hemophiliac dogs infected with a retroviral vector expressing factor IX shows improved levels of clotting and thromboplastin times for greater than 5 months after treatment.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of claims 8 and 10 of U.S. Patent No. 6,177,681 in view of Mehigh et al. as applied to claims 33-35, 38, 42, 43, 46-49, and 51-55 above to express a therapeutic protein because both Kay et al. and Longmore et al. show that retroviral vectors may be used to express therapeutically effective levels of a recombinant protein in an animal.

1. Claim 58 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8 and 10 of U.S. Patent No. 6,177,681 in view of Couture et al. as applied to claims 19, 20, 21, 23-25, 56, 57, 61, 65, 66, 68-72, and 74-78 above and further in view of Mee et al.

Claims 8 and 10 of U.S. Patent No. 6,177,681 in view of Couture et al. as applied to claims 19, 20, 21, 23-25, 56, 57, 61, 65, 66, 68-72, and 74-78 above do not show a retroviral vector with a mouse mammary tumor virus promoter.

Mee et al. shows a retroviral vector comprising a mouse mammary tumor virus LTR, and that the LTR expressed a gene after induction with dexamethasone. Mee et al. state on page 292 that their vector is a potentially powerful tool for the manipulation of gene expression in a variety of cell types.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of claims 8 and 10 of U.S. Patent No. 6,177,681 in view of Couture et al. as applied to claims 19, 20, 21, 23-25, 56, 57, 61, 65, 66, 68-72, and 74-78 above by insertion of an MMTV promoter region in a deleted 3' U3 region of a retroviral vector because Mee et al. show that their LTR promoter may be used to manipulate gene expression in a variety of cell types.

2. Claims 60 and 62 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8 and 10 of U.S. Patent No. 6,177,681 in view of Couture et al. as applied to claims 19, 20, 21, 23-25, 56, 57, 61, 65, 66, 68-72, and 74-78 above and further in view of Price et al.

Claims 8 and 10 of U.S. Patent No. 6,177,681 in view of Couture et al. as applied to claims 19, 20, 21, 23-25, 56, 57, 61, 65, 66, 68-72, and 74-78 above do not show a retroviral vector derived from a BAG vector or comprising a beta-galactosidase gene.

Price et al. shows a BAG retroviral vector comprising a beta galactosidase reporter gene, and that the vector can be used to identify cells and progeny of cells infected with the vector.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of claims 8 and 10 of U.S. Patent No. 6,177,681 in view of Couture et al. as applied to claims 19, 20, 21, 23-25, 56, 57, 61, 65, 66, 68-72, and 74-78 above by basing the construction on a BAG vector of Price et al. because Price et al shows that a vector with a beta-galactosidase reporter gene may be used to identify cells and progeny of cells infected with the vector.

3. Claims 63 and 64 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8 and 10 of U.S. Patent No. 6,177,681 in view of Couture et al. as applied to claims 19, 20, 21, 23-25, 56, 57, 61, 65, 66, 68-72, and 74-78 above and further in view of Miller et al. and Paganiban '84.

Claims 8 and 10 of U.S. Patent No. 6,177,681 in view of Couture et al. as applied to claims 19, 20, 21, 23-25, 56, 57, 61, 65, 66, 68-72, and 74-78 above do not show retroviral vectors that comprise an altered retroviral gene or a partially deleted sequence involved in integration of retroviruses.

Miller et al. shows in the introduction on page 980 that it is desirable to have retroviral vectors that cannot recombine with retroviral sequences in packaging cell lines to yield contaminating helper virus. In figure 2 Miller et al. shows that extensive deletions in their retroviral vectors to block recombination with packaging cell line retroviral sequences, including deletion of the pol gene, but that their vectors retain the phi+ packaging sequence.

Panganiban '84 shows that the 3' end of the pol gene encodes the int locus that is required for integration of the reverse transcribed retroviral genome to form a provirus.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to include a deletion of at least the pol gene in the retroviral vector of claims 8 and 10 of U.S. Patent No. 6,177,681 in view of Couture et al. as applied to claims 19, 20, 21, 23-25, 56, 57, 61, 65, 66, 68-72, and 74-78 above because Miller et al. shows that prevention of recombination with packaging cell retroviral sequences is desirable and may be achieved by

deletion of viral genes, including the pol gene. Panganiban '84 shows that deletion of the pol gene also deletes the integration site.

20. Claim 73 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8 and 10 of U.S. Patent No. 6,177,681 in view of Couture et al. as applied to claims 19, 20, 21, 23-25, 56, 57, 61, 65, 66, 68-72, and 74-78 above and further in view of Longmore et al. and Kay et al.

Claims 8 and 10 of U.S. Patent No. 6,177,681 in view of in view of Couture et al. as applied to claims 19, 20, 21, 23-25, 56, 57, 61, 65, 66, 68-72, and 74-78 above do not show a vector that can be used as a therapeutic composition.

Longmore et al show in the abstract that mice infected with a retroviral vector expressing the erythropoietin receptor had increased platelet counts and splenic megakaryocytes.

Kay et al. shows in the abstract and throughout that hemophiliac dogs infected with a retroviral vector expressing factor IX shows improved levels of clotting and thromboplastin times for greater than 5 months after treatment.

4. It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of claims 8 and 10 of U.S. Patent No. 6,177,681 in view of Couture et al. as applied to claims 19, 20, 21, 23-25, 56, 57, 61, 65, 66, 68-72, and 74-78 above to express a therapeutic protein because both Kay et al. and Longmore et al. show that retroviral vectors may be used to express therapeutically effective levels of a recombinant protein in an animal.

5. Claims 1, 5, 11, 17, 19-25, 28, 29, 31, 32, 56, 57, 61, 66, 68-72, and 74-77 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 7,022,319 in view of Couture et al.

The claims are drawn to a murine leukemia virus retroviral vector with a partially deleted U3 region in which is inserted a polylinker comprising a heterologous promoter. In some embodiments the vector comprises a regulatory element, a promoter, a therapeutic gene, or a heterologous retroviral promoter, or a target-cell specific promoter. In some embodiments the vector is in a kit further comprising a packaging cell. Some embodiments are drawn to retroviral particles or RNA produced by packaging cells infected with the vector, or a packaging cell infected with the vector, or a provirus produced by the vector after infection. In some embodiments the packaging cell lines are PA317 or GP&E86. Some embodiments are drawn to a method of infecting cells with the retroviral vector

Claims 1-20 of U.S. Patent No. 7,022,319 show a retroviral vector with a partially deleted U3 region in which is inserted a polylinker comprising a heterologous promoter or regulatory element. The vector comprises a therapeutic gene. Some embodiments are drawn to combinations of packaging cell lines and retroviral vectors, retroviral particles, retroviral RNA, retroviral provirus, and methods of infecting cells with the retroviral vector.

Claims 1-20 of U.S. Patent No. 7,022,319 do not show packaging cell lines PA317 or GP&E86, or a vector comprising a heterologous retroviral promoter or a target-cell specific promoter.

Couture et al. (Reference AS in the Form PTO-1449 filed 9/23/97) shows retroviral vectors comprising a substitution of a portion of the 3' U3 region with the corresponding region of 5 different murine retroviruses, including leukemia and sarcoma retroviruses. Couture et al. shows in the abstract that the inserted region comprises an enhancer regulatory element and a promoter. Couture et al. shows on page 669 column 2 that the first 40 nucleotides of the original vector are retained in the substitution of the U3 region. The vector of Couture comprises a chloramphenicol acetyl transferase marker gene operably linked to the recombinant reporter and a neomycin resistance gene. Couture et al. shows in the abstract that after packaging, the substituted U3 region appears at the 5' LTR and serves as a promoter for all genes in the body of the vector, and that different LTR constructs were preferentially expressed in specific cell types. Couture et al. states in the second paragraph of the Results section on page 669 that U3 regions are bound by cellular factors. Couture et al. shows in Table 3 that their chimeric LTR promoters are active in a cell type specific manner. Couture et al. state on page 670 that promoter suppression or interference may occur within retroviral vectors containing internal promoter elements. Couture et al. states on page 667 that retroviral vectors with target cell specificity have utility in gene therapy protocols. Couture et al. shows the use of packaging cell lines PA317 and GP&E86 on page 669 to package their retroviral vectors into retroviral particles. Couture et al. show on page 668, at the top of the first column that retroviral expression controlled by the LTR occurs after integration of a provirus in infected cells.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vectors of claims 1-20 of U.S. Patent No. 7,022,319 by

addition of a heterologous retroviral promoter because Couture et al. shows that such retroviral vectors allow for control of the cell type in which the vector genes are expressed. It would have been further obvious to use the packaging cell lines PA317 and GP&E86 on page 669 to package their retroviral vectors into retroviral particles because Couture et al. show that those packaging cell lines are useful to package retroviral vectors.

6. Claims 7, 16, 58, and 65 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 7,022,319 in view of Couture et al. as applied to claims 1, 5, 11, 17, 19-25, 28, 29, 31, 32, 56, 57, 61, 66, 68-72, and 74-77 above and further in view of Mee et al.

Claims 1-20 of U.S. Patent No. 7,022,319 in view of Couture et al. as applied to claims 1, 5, 11, 17, 19-25, 28, 29, 31, 32, 56, 57, 61, 66, 68-72, and 74-77 above do not show a retroviral vector with a mouse mammary tumor virus promoter or a promoter regulatable by transacting molecules.

Mee et al. shows a retroviral vector comprising a mouse mammary tumor virus LTR, and that the LTR expressed a gene after induction with dexamethasone. Mee et al. state on page 292 that their vector is a potentially powerful tool for the manipulation of gene expression in a variety of cell types.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of claims 1-20 of U.S. Patent No. 7,022,319 in view of Couture et al. as applied to claims 1, 5, 11, 17, 19-25, 28, 29, 31, 32, 56, 57, 61, 66, 68-72, and 74-77 above by insertion of an MMTV promoter region in a deleted 3' U3 region of a retroviral

vector because Mee et al. show that their LTR promoter may be used to manipulate gene expression in a variety of cell types.

7. Claims 10, 12, 60, and 62 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 7,022,319 in view of Couture et al. as applied to claims 1, 5, 11, 17, 19-25, 28, 29, 31, 32, 56, 57, 61, 66, 68-72, and 74-77above and further in view of Price et al.

Claims 1-20 of U.S. Patent No. 7,022,319 in view of Couture et al. as applied to claims 1, 5, 11, 17, 19-25, 28, 29, 31, 32, 56, 57, 61, 66, 68-72, and 74-77 above do not show a retroviral vector derived from a BAG vector.

Price et al. shows a BAG retroviral vector comprising a beta galactosidase reporter gene, and that the vector can be used to identify cells and progeny of cells infected with the vector.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of claims 1-20 of U.S. Patent No. 7,022,319 in view of Couture et al. as applied to claims 1, 5, 11, 17, 19-25, 28, 29, 31, 32, 56, 57, 61, 66, 68-72, and 74-77 above by basing the construction on a BAG vector of Price et al. because Price et al shows that a vector with a beta-galactosidase reporter gene may be used to identify cells and progeny of cells infected with the vector.

8. Claims 13, 14, 63, 64 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 7,022,319 in view of Couture et al. as applied to claims 1, 5, 11, 17, 19-25, 28, 29, 31, 32, 56, 57, 61, 66, 68-72, and 74-77 above and further in view of Miller et al. and Paganiban '84.

Claims 1-20 of U.S. Patent No. 7,022,319 in view of Couture et al. as applied to claims 1, 5, 11, 17, 19-25, 28, 29, 31, 32, 56, 57, 61, 66, 68-72, and 74-77 above do not show retroviral vectors that comprise an altered retroviral gene or a partially deleted sequence involved in integration of retroviruses.

Miller et al. shows in the introduction on page 980 that it is desirable to have retroviral vectors that cannot recombine with retroviral sequences in packaging cell lines to yield contaminating helper virus. In figure 2 Miller et al. shows that extensive deletions in their retroviral vectors to block recombination with packaging cell line retroviral sequences, including deletion of the pol gene, but that their vectors retain the phi+ packaging sequence.

Panganiban '84 shows that the 3' end of the pol gene encodes the int locus that is required for integration of the reverse transcribed retroviral genome to form a provirus.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to include a deletion of at least the pol gene in the retroviral vector of claims 1-20 of U.S. Patent No. 7,022,319 in view of Couture et al. as applied to claims 1, 5, 11, 17, 19-25, 28, 29, 31, 32, 56, 57, 61, 66, 68-72, and 74-77 above because Miller et al. shows that prevention of recombination with packaging cell retroviral sequences is desirable and may be achieved by deletion of viral genes, including the pol gene. Panganiban '84 shows that deletion of the pol gene also deletes the integration site.

9. Claims 33-35, 38, 43, 45-49, 51-55, and 78 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No.

7,022,319 in view of Couture et al. as applied to claims 1, 5, 11, 17, 19-25, 28, 29, 31, 32, 56, 57, 61, 66, 68-72, and 74-77 above and further in view of Mehigh et al.

Claims 1-20 of U.S. Patent No. 7,022,319 in view of Couture et al. as applied to claims 1, 5, 11, 17, 19-25, 28, 29, 31, 32, 56, 57, 61, 66, 68-72, and 74-77 above do not show retroviral vectors comprising a cellular whey acidic protein promoter.

Mehigh et al. shows a retroviral vector comprising a whey acidic acid protein (WAP) promoter. Mehigh et al. states in the abstract that their vector allows for inducible expression from the WAP promoter of an operably linked gene in MBDK cells and may prove useful as a delivery system for peptides in cattle to increase milk production.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of Couture et al. as applied to claims 1, 5, 11, 17, 19-25, 28, 29, 31, 32, 56, 57, 61, 66, 68-72, and 74-77 above by insertion of a WAP promoter region in a deleted 3' U3 region of a retroviral vector because Mehigh et al. shows that such vectors are inducibly expressed and may allow for increased milk production in cattle.

10. Claims 7 and 39 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 7,022,319 in view of Couture et al. in view of Mehigh et al. as applied to claims 33-35, 38, 43, 45-49, 51-55, and 78 above and further in view of Price et al.

Claims 1-20 of U.S. Patent No. 7,022,319 in view of Couture et al. in view of Mehigh et al. as applied to claims 33-35, 38, 43, 45-49, 51-55, and 78 above do not show a retroviral vector derived from a BAG vector.

Price et al. shows a BAG retroviral vector comprising a beta galactosidase reporter gene, and that the vector can be used to identify cells and progeny of cells infected with the vector.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of claims 1-20 of U.S. Patent No. 7,022,319 in view of Couture et al. in view of Mehigh et al. as applied to claims 33-35, 38, 43, 45-49, 51-55, and 78 above by basing the construction on a BAG vector of Price et al. because Price et al shows that a vector with a beta-galactosidase reporter gene may be used to identify cells and progeny of cells infected with the vector.

11. Claims 40 and 41 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 7,022,319 in view of Couture et al. in view of Mehigh et al. as applied to claims 33-35, 38, 43, 45-49, 51-55, and 78 above and further in view of Miller et al. and Paganiban '84.

Claims 1-20 of U.S. Patent No. 7,022,319 in view of Couture et al. in view of Mehigh et al. as applied to claims 33-35, 38, 43, 45-49, 51-55, and 78 above do not show retroviral vectors that comprise an altered retroviral gene or a partially deleted sequence involved in integration of retroviruses.

Miller et al. shows in the introduction on page 980 that it is desirable to have retroviral vectors that cannot recombine with retroviral sequences in packaging cell lines to yield contaminating helper virus. In figure 2 Miller et al. shows that extensive deletions in their retroviral vectors to block recombination with packaging cell line retroviral sequences, including deletion of the pol gene, but that their vectors retain the phi+ packaging sequence.

Panganiban '84 shows that the 3' end of the pol gene encodes the int locus that is required for integration of the reverse transcribed retroviral genome to form a provirus.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to include a deletion of at least the pol gene in the retroviral vector of claims 1-20 of U.S. Patent No. 7,022,319 in view of Couture et al. in view of Mehigh et al. as applied to claims 33-35, 38, 43, 45-49, 51-55, and 78 above because Miller et al. shows that prevention of recombination with packaging cell retroviral sequences is desirable and may be achieved by deletion of viral genes, including the pol gene. Panganiban '84 shows that deletion of the pol gene also deletes the integration site.

12. Claim 42 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 7,022,319 in view of Couture et al. in view of Mehigh et al. as applied to claims 33-35, 38, 43, 45-49, 51-55, and 78 above and further in view of Mee et al.

Claims 1-20 of U.S. Patent No. 7,022,319 in view of Couture et al. in view of Mehigh et al. as applied to claims 33-35, 38, 43, 45-49, 51-55, and 78 above do not show a retroviral vector with a mouse mammary tumor virus promoter or a promoter regulatable by transacting molecules.

Mee et al. shows a retroviral vector comprising a mouse mammary tumor virus LTR, and that the LTR expressed a gene after induction with dexamethasone. Mee et al. state on page 292 that their vector is a potentially powerful tool for the manipulation of gene expression in a variety of cell types.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of claims 1-20 of U.S. Patent No. 7,022,319 in view of Couture et al. in view of Mehigh et al. as applied to claims 33-35, 38, 43, 45-49, 51-55, and 78 above by insertion of an MMTV promoter region in a deleted 3' U3 region of a retroviral vector because Mee et al. show that their LTR promoter may be used to manipulate gene expression in a variety of cell types.

21. Claims 26 and 73 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 7,022,319 in view of Couture et al. as applied to claims 1, 5, 11, 17, 19-25, 28, 29, 31, 32, 56, 57, 61, 66, 68-72, and 74-77 above and further in view of Longmore et al. and Kay et al.

Claims 1-20 of U.S. Patent No. 7,022,319 in view of Couture et al. as applied to claims 1, 5, 11, 17, 19-25, 28, 29, 31, 32, 56, 57, 61, 66, 68-72, and 74-77 above show a retroviral vector that comprises a gene encoding a therapeutic protein, but do not explicitly show a retroviral vector that can be used as a therapeutic composition.

Longmore et al show in the abstract that mice infected with a retroviral vector expressing the erythropoietin receptor had increased platelet counts and splenic megakaryocytes.

Kay et al. shows in the abstract and throughout that hemophiliac dogs infected with a retroviral vector expressing factor IX shows improved levels of clotting and thromboplastin times for greater than 5 months after treatment.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of claims 1-20 of U.S. Patent No. 7,022,319 in view of

Couture et al. as applied to claims 1, 5, 11, 17, 19-25, 28, 29, 31, 32, 56, 57, 61, 66, 68-72, and 74-77 above to express a therapeutic protein because both Kay et al. and Longmore et al. show that retroviral vectors may be used to express therapeutically effective levels of a recombinant protein in an animal.

22. Claim 50 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 7,022,319 in view of Couture et al. in view of Mehigh et al. as applied to claims 33-35, 38, 43, 45-49, 51-55, and 78 above and further in view of Longmore et al. and Kay et al.

Claims 1-20 of U.S. Patent No. 7,022,319 in view of Couture et al. in view of Mehigh et al. as applied to claims 33-35, 38, 43, 45-49, 51-55, and 78 above show a retroviral vector that comprises a gene encoding a therapeutic protein, but do not explicitly show a retroviral vector that can be used as a therapeutic composition.

Longmore et al show in the abstract that mice infected with a retroviral vector expressing the erythropoietin receptor had increased platelet counts and splenic megakaryocytes.

Kay et al. shows in the abstract and throughout that hemophiliac dogs infected with a retroviral vector expressing factor IX shows improved levels of clotting and thromboplastin times for greater than 5 months after treatment.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of claims 1-20 of U.S. Patent No. 7,022,319 in view of Couture et al. in view of Mehigh et al. as applied to claims 33-35, 38, 43, 45-49, 51-55, and 78 above to express a therapeutic protein because both Kay et al. and Longmore et al. show that

retroviral vectors may be used to express therapeutically effective levels of a recombinant protein in an animal.

23. Claims 1, 5, 7, 11, 15, 17, 19-26, 28, 29, 31-35, 38, 43, 45-58, 61, 66, and 68-78 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 4, 8-10, and 13 of U.S. Patent No. 7,074,398 in view of Couture et al.

The claims are drawn to a murine leukemia virus vector with a partially deleted U3 region in which is inserted a polylinker comprising a heterologous promoter or a target-cell specific promoter, or a whey acidic protein promoter or a mouse mammary tumor virus promoter. In some embodiments the vector comprises a regulatory element, a cellular or therapeutic gene, or a heterologous retroviral promoter. In some embodiments the vector is in a kit further comprising a packaging cell. Some embodiments are drawn to retroviral particles produced by packaging cells infected with the vector or a packaging cell infected with the vector, or a provirus produced by the vector after infection. In some embodiments the packaging cell lines are PA317 or GP&E86. In some embodiments the vector is in a pharmaceutical composition.

Claims 1, 3, 4, 8-10, and 13 of U.S. Patent No. 7,074,398 show a retroviral vector with a partially deleted U3 region in which is inserted a polylinker comprising a heterologous promoter or regulatory element that is target cell specific. The vector comprises a therapeutic gene. In some embodiments the vector comprises target-cell specific promoter, or a whey acidic protein promoter or a mouse mammary tumor virus promoter. In some embodiments a packaging cell

produces the vector, or the retroviral vector are in particles, or the retroviral particles are in a pharmaceutical composition.

Claims 1, 3, 4, 8-10, and 13 of U.S. Patent No. 7,074,398 do not show a kit comprising a packaging cell and a vector, or packaging cell lines PA317 or GP&E86, or explicitly a provirus in an infected cell, or explicitly a vector comprising a heterologous retroviral promoter.

Couture et al. (Reference AS in the Form PTO-1449 filed 9/23/97) shows retroviral vectors comprising a substitution of a portion of the 3' U3 region with the corresponding region of 5 different murine retroviruses, including leukemia and sarcoma retroviruses. Couture et al. shows in the abstract that the inserted region comprises an enhancer regulatory element and a promoter. Couture et al. shows on page 669 column 2 that the first 40 nucleotides of the original vector are retained in the substitution of the U3 region. The vector of Couture comprises a chloramphenicol acetyl transferase marker gene operably linked to the recombinant reporter and a neomycin resistance gene. Couture et al. shows in the abstract that after packaging, the substituted U3 region appears at the 5' LTR and serves as a promoter for all genes in the body of the vector, and that different LTR constructs were preferentially expressed in specific cell types. Couture et al. states in the second paragraph of the Results section on page 669 that U3 regions are bound by cellular factors. Couture et al. shows in Table 3 that their chimeric LTR promoters are active in a cell type specific manner. Couture et al. state on page 670 that promoter suppression or interference may occur within retroviral vectors containing internal promoter elements. Couture et al. states on page 667 that retroviral vectors with target cell specificity have utility in gene therapy protocols. Couture et al. shows the use of packaging cell lines PA317 and

GP&E86 on page 669 to package their retroviral vectors into retroviral particles. Couture et al. show on page 668, at the top of the first column that retroviral expression controlled by the LTR occurs after integration of a provirus in infected cells.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vectors of claims 1, 3, 4, 8-10, and 13 of U.S. Patent No. 7,074,398 by addition of a heterologous retroviral promoter because Couture et al. shows that such retroviral vectors allow for control of the cell type in which the vector genes are expressed. It would have been further obvious to make a kit of the packaging cell and vector because such a kit would allow for convenience in infecting the packaging cell with the vector. It would have been further obvious to use the packaging cell lines PA317 and GP&E86 on page 669 to package their retroviral vectors into retroviral particles because Couture et al. show that those packaging cell lines are useful to package retroviral vectors.

24. Claims 10, 37, and 60 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 4, 8-10, and 13 of U.S. Patent No. 7,074,398 in view of Couture et al. as applied to claims 1, 5, 7, 11, 15, 17, 19-26, 28, 29, 31-35, 38, 43, 45-58, 61, 66, and 68-78 above and further in view of Price et al.

Claims 1, 3, 4, 8-10, and 13 of U.S. Patent No. 7,074,398 in view of Couture et al. as applied to claims 1, 5, 7, 11, 15, 17, 19-26, 28, 29, 31-35, 38, 43, 45-58, 61, 66, and 68-78 above do not show a vector that is a BAG vector.

Price et al. shows a BAG retroviral vector comprising a beta galactosidase reporter gene, and that the vector can be used to identify cells and progeny of cells infected with the vector.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of claims 1, 3, 4, 8-10, and 13 of U.S. Patent No. 7,074,398 in view of Couture et al. as applied to claims 1, 5, 7, 11, 15, 17, 19-26, 28, 29, 31-35, 38, 43, 45-58, 61, 66, and 68-78 above by basing the construction on a BAG vector of Price et al. because Price et al shows that a vector with a beta-galactosidase reporter gene may be used to identify cells and progeny of cells infected with the vector.

13. Claims 10, 37, and 60 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 4, 8-10, and 13 of U.S. Patent No. 7,074,398 in view of Couture et al. as applied to claims 1, 5, 7, 11, 15, 17, 19-26, 28, 29, 31-35, 38, 43, 45-58, 61, 66, and 68-78 above and further in view of Miller et al. and Paganiban '84.

Claims 1, 3, 4, 8-10, and 13 of U.S. Patent No. 7,074,398 in view of Couture et al. as applied to claims 1, 5, 7, 11, 15, 17, 19-26, 28, 29, 31-35, 38, 43, 45-58, 61, 66, and 68-78 above do not show retroviral vectors that comprise an altered retroviral gene or a partially deleted sequence involved in integration of retroviruses.

Miller et al. shows in the introduction on page 980 that it is desirable to have retroviral vectors that cannot recombine with retroviral sequences in packaging cell lines to yield contaminating helper virus. In figure 2 Miller et al. shows that extensive deletions in their retroviral vectors to block recombination with packaging cell line retroviral sequences, including deletion of the pol gene, but that their vectors retain the phi+ packaging sequence.

Panganiban '84 shows that the 3' end of the pol gene encodes the int locus that is required for integration of the reverse transcribed retroviral genome to form a provirus.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to include a deletion of at least the pol gene in the retroviral vector of claims 1, 3, 4, 8-10, and 13 of U.S. Patent No. 7,074,398 in view of Couture et al. as applied to claims 1, 5, 7, 11, 15, 17, 19-26, 28, 29, 31-35, 38, 43, 45-58, 61, 66, and 68-78 above because Miller et al. shows that prevention of recombination with packaging cell retroviral sequences is desirable and may be achieved by deletion of viral genes, including the pol gene. Panganiban '84 shows that deletion of the pol gene also deletes the integration site.

14. Claims 10, 37, and 60 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 4, 8-10, and 13 of U.S. Patent No. 7,074,398 in view of Couture et al. as applied to claims 1, 5, 7, 11, 15, 17, 19-26, 28, 29, 31-35, 38, 43, 45-58, 61, 66, and 68-78 above as evidenced by Mee et al.

Claims 1, 3, 4, 8-10, and 13 of U.S. Patent No. 7,074,398 in view of Couture et al. as applied to claims 1, 5, 7, 11, 15, 17, 19-26, 28, 29, 31-35, 38, 43, 45-58, 61, 66, and 68-78 above show a retroviral vector with a mouse mammary tumor virus promoter but do not explicitly show that the mouse mammary tumor virus promoter is regulated by a trans-acting factor.

Mee et al. shows a retroviral vector comprising a mouse mammary tumor virus LTR, and that the LTR expressed a gene after induction with dexamethasone. Mee et al. state on page 292 that their vector is a potentially powerful tool for the manipulation of gene expression in a variety of cell types. Mee et al. therefore shows that the embodiment of Claims 1, 3, 4, 8-10, and 13 of U.S. Patent No. 7,074,398 that comprises a mouse mammary tumor virus promoter inherently comprises a promoter that is regulated by a trans-acting factor.

Conclusion

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca whose telephone number is 571 272-0714. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie A. Moran can be reached on 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/John S. Brusca/

Primary Examiner

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